

II. Amendments to the Specification

Please replace paragraph [0005] with the following amended paragraph [0005]:

[0005] A large panel of therapeutic agents is known for treating cancer. Anti-neoplastics include, but are not limited to, those of the following TABLE 1;

TABLE 1

| | |
|-------------------------------------|---|
| <u>Alkylating Agents</u> | <i>Alkyl Sulphonates</i> |
| | busulfan |
| | <i>Ethylene Imines</i> |
| | thiotepa |
| | <i>Nitrogen Mustard Analogues</i> |
| | chlorambucil cyclophosphamide |
| | estramustine sodium phosphate |
| | ifosfamide |
| | mechlorethamine hydrochloride |
| | melphalan |
| | <i>Nitrosoureas</i> |
| | carmustine |
| | lomustine |
| | streptozocin |
| | <i>Platinum-containing Compounds</i> |
| | carboplatin |
| | cisplatin |
| <u>Antimetabolites</u> | <i>Folic Acid Analogues</i> |
| | methotrexate sodium |
| | <i>Purine Analogues</i> |
| | cladribine |
| | mecaptopurine |
| | thioguanine |
| | <i>Pyrimidine Analogues</i> |
| | cytarabine |
| | fluorouracil |
| | <i>Urea Derivatives</i> |
| | hydroxyurea |
| <u>Cytotoxic Antibiotics</u> | <i>Anthracyclines</i> |
| | daunorubicin |
| | doxorubicin hydrochloride |
| | epirubicin hydrochloride |
| | idarubicin hydrochloride |
| | <i>Actinomycins</i> |

| | |
|---|---|
| | dactinomycin |
| | <i>Various Cytotoxic Antibiotics</i> |
| | bleomycin sulfate |
| | mitomycin |
| | mitotane |
| | mitoxanthrone hydrochloride |
| <u>Plant Alkaloids and Other Natural Products</u> | <i>Epipodphyllotoxins</i> |
| | etoposide |
| | teniposide |
| | <i>Taxanes</i> |
| | docetaxel |
| | paclitaxel |
| | <i>Vinca Alkaloids and Analogues</i> |
| | vinblastine sulfate |
| | vincristine sulfate |
| | vindesine sulfate |
| | vinorelbine tartrate |
| <u>Various Anti-Neoplastics</u> | altretamine |
| | amsacrine |
| | l-asparaginase |
| | dacarbazine |
| | fludarabine phosphate |
| | porfimer sodium |
| | procarbazine hydrochloride |
| | tretinoin (all-trans retinoic acid), systemic |
| <u>Anti-angiogenics</u> | Marimastat |
| | Suramin |
| | TNP 470 |
| | Thalidomide, and |
| <u>Radioterapeutics</u> <u>Radiotherapeutics</u> | |

Please replace paragraph [0011] with the following amended paragraph [0011]:

[0011] The overall advantageous contribution of the cartilage extract is in addition to the efficacy of the anti-neoplastic and protection against toxic side effects.

Please replace paragraph [0015] with the following amended paragraph [0015]:

[0015] In a first preferred embodiment, the anti-tumor amount of the anti-neoplastic agent is a sub-optimal dose thereof, and the amount of cartilage extract given in combination adds anti-tumor efficacy to the anti-neoplastic ~~agency~~ agent with no increase, even better a decrease, of toxic side effects inherent to the administration of higher dose of the antineoplastic, which would have an anti-tumor efficacy equivalent to the combined anti-tumor therapy.

Please replace paragraph [0018] with the following amended paragraph [0018]:

[0018] The anti-neoplastic agent may be busulfan, thiotepa, chlorambucil, cyclophosphamide, estramustine sodium phosphate, ifosfamide, mechlorethamine hydrochloride, melphalan, carmustine, lomustine, streptozocin, carboplatin, cisplatin, methotrexate sodium, cladribine, mercaptopurine, thioguanine, cytarabine, fluorouracil, hydroxyurea, daunorubicin, doxorubicin hydrochloride, epirubicin hydrochloride, idarubicin hydrochloride, dactinomycin, bleomycin sulfate, mitomycin, mitotane, mitoxantrone hydrochloride, etoposide, teniposide, docetaxel, paclitaxel, vinglaxine sulfate, vincristine sulfate, vindesine sulfate, vinorelbine tartrate, altretamine, amsacrine, 1-asparaginase, dacarbazine, fludarabine phosphate, porfimer sodium, procarbazine hydrochloride, tretinoid (all-trans retinoic acid), marimastat, suramin, TNP 470, thalidomide, or ~~radiotherapy~~ radiotherapeutics.

Please replace paragraph [0027] with the following amended paragraph [0027]:

[0027] FIG. 1 shows the reduction in the number of metastases in LLC mouse tumor model. Increasing doses of cartilage liquid extract (-X) have been orally administered to LLC mice alone or in combination with cisplatin (CDDP). ~~CDDP~~ CDDP alone has also been tested alone. The control represents saline-treated mice.

Please replace paragraph [0037] with the following amended paragraph [0037]:

[0037] The anti-tumor potential of cartilage extract was studied in a mouse mammary adenocarcinoma model (allograft). DA3 cells (1×10^6) were inoculated subcutaneously into the right flank of adult BALB/c mice. These cells originate from a murine mammary adenocarcinoma induced by 7,12-dimethylbenzanthracene (DMBA). DA3 is a non-or low-metastatic murine mammary carcinoma (O. Medina, J. Natl. Cancer Inst., 1969, 42: 303-310; *ibid.*, 1976, 57: 1185-1189). Inoculated cells grow slowly *in vivo* and form a solid tumor with a low metastatic prognosis. DA3 cells were maintained in RPMI 1640 medium supplemented with 50 μ M mercaptoethanol, 0.2 mM Hepes buffer solution, 1 mM Na-pyruvate, 2 mM L-glutamine, 0.1 mM non-essential amino acids, 10 mM vitamins, 10% fetal bovine serum and 1% penicillin streptomycin. The cells were incubated at 37°C. in atmosphere containing 5% CO₂. Under these conditions, DA3 cells proliferate but do not differentiate. For tumor induction, cells were grown to 70% confluence in complete medium and then collected using trypsin-EDTA solution. Cells were centrifuged, washed three times with phosphate buffer solution (D-PBS, Ca⁺⁺ and Mg⁺⁺ free), and resuspended at a dilution of 1×10^7 cells/ml. Mice (n=15) were inoculated with 0.1 ml of cell suspension and were given daily oral administration of cartilage extract or a placebo (saline solution). The treatments began the day of DA3 cell inoculation or 7 days later, after randomization of animals. Various concentrations of cartilage extract were tested. Cartilage extract dose levels are expressed as the amount of cartilage extract dry weight administered per kg of body weight.

Please replace paragraph [0041] with the following amended paragraph [0041]:

[0041] We have verified the anti-tumor efficacy and the protective effect of cartilage extract by testing a combination of diverse concentrations of cartilage liquid extract alone and in combination with cisplatin (~~COOP~~) (CDDP), in the Lewis lung carcinoma model (LLC).

Please replace paragraph [0043] with the following amended paragraph [0043]:

[0043] In a first experiment, five injections of CDDP were given intraperitoneally every three days (1, 2 and 3 mg/Kg). Cartilage extract was given per as daily (31, 125 and 500 mg/Kg). Saline was given as a control. Results are summarized in Table 2.

TABLE 2

| CDDP (mg/kg) | | Percent reduction from control | | | |
|--------------|----|--------------------------------|-----|-----|--|
| | | 60 | 69 | 85 | |
| 3 | 54 | 46 | 69 | 73 | |
| 2 | 35 | 39 | 69 | 65 | |
| 1 | 19 | 23 | 65 | 69 | |
| 0 | 0 | 31 | 125 | 500 | |
| | | Cartilage extract (mg/kg) | | | |